

Changing pattern of gastric cancer in Oxfordshire

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Abstract

This study compares the incidence rates of histologically confirmed gastric carcinoma in Oxfordshire in two five year periods (1960-64, 1984-88). Data were available for 215 patients in the first period, and 200 in the second. The overall incidence fell from 18/100 000 to 15/100 000 but when analysed for site, the incidence of antral tumours fell from 10 to 4.5/100 000. In contrast, there was an increase from 2.8 to 5.2/100 000 of tumours of the cardia. These changes were more pronounced in men. There was a marked association between smoking and tumours of the cardia (relative risk 4.5). *Helicobacter pylori* was associated with 37.5% of tumours in the 1960s series compared with 25% in the later series. The changing patterns of incidence of gastric carcinoma may, in part, be related to changes in smoking habits and perhaps a change in incidence of *H pylori* infection.

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Although the incidence of gastric cancer is declining worldwide, especially in the developed countries of North America, Europe, and Japan,¹⁻⁴ there have been several recent reports showing that there has been an increase in carcinomas of the cardia compared with carcinomas in the antrum.⁵⁻¹²

Cancer of the cardia is different in the sex ratio, histological type, prognosis, and in relation to aetiological factors such as the consumption of alcohol and tobacco, when compared with gastric cancer in other locations.¹³⁻¹⁶ These differences have led some investigators to consider cancer of the cardia as a separate entity.¹⁷

The reasons for the apparent change in relative incidence at different sites are poorly understood and there is controversy about whether the increase of cardia cancer represents an absolute increment or whether the apparent increase is related to a decreased incidence of antral tumours.

The aim of this study is to compare the incidence rates of gastric cancer in two five year periods (1960-64 and 1984-88) by site, sex, and age, histological type, the nature of the inflammation adjacent to the tumour, and alcohol and tobacco consumption. The association between gastric histopathology and *Helicobacter pylori* was also investigated.

Methods

The slides of all consecutive histologically confirmed gastric carcinomas of two five year periods diagnosed at the Radcliffe Infirmary between 1960-64 (n=215, 154 men and 61 women) and at the John Radcliffe Hospital

between 1984-88 (n=200, 138 men and 62 women) were reviewed and compared with respect to sex, age, site of the tumour, gross morphology, histological classification, differentiation, and the pattern of inflammation in the surrounding mucosa.

The location, staging, and gross morphology of the cancers were classified according to the criteria of the Japanese Society for Gastric Cancer,¹⁸ and the revised tumour node metastasis classification.¹⁹ In tumours affecting the cardia and the lower oesophagus, the tumour was included in the series if the majority of the tumour was gastric. Adenocarcinomas arising from Barrett's epithelium were excluded.

All the available histology was analysed by an independent pathologist (NAS). Tumours were typed according to the Lauren classification into intestinal, diffuse and mixed types.²⁰ A tumour was considered mixed if the minority component comprised more than 20% of the total tumour mass according to the criteria of the British Stomach Cancer Group (Levison DA, personal communication). The World Health Organization criteria were used to assess the degree of differentiation.²¹

The presence of inflammatory changes in the mucosa surrounding the cancer were assessed according to the method of Whitehead *et al*.²²

(i) No significant inflammation; (ii) chronic superficial gastritis; (iii) chronic atrophic gastritis; (iv) chronic active gastritis.

Chronic atrophic gastritis and chronic active gastritis were graded as mild, moderate and severe.

The presence of *H pylori* was determined using a modified Giemsa stain. Where possible, the presence or absence of the organisms was assessed in the mucosa surrounding the tumour as well as in the tumour itself. *Helicobacter* like organisms were scored as absent, scanty, moderate or numerous. The degree of intestinal metaplasia was classified as absent, incomplete, complete or mixed according to the criteria of Filipe and Jass.²³ In a retrospective study such as this, it is impossible to fully assess the type of intestinal metaplasia and therefore for analysis intestinal metaplasia was simply judged to be present (+) or absent (-).

Some caution should be applied when comparing histological data from the two time periods. In the earlier series, specimens available for histological review were mostly operative resection specimens (95.4%), whereas in the later series only 70.3% were operative specimens and 29.7% biopsy specimens.

For the 1984-88 series, data on alcohol and tobacco consumption were recorded in the hospital records but there were insufficient data on the quantity of consumption to allow detailed analysis. Recorded data in the earlier series were incomplete and no analysis was attempted.

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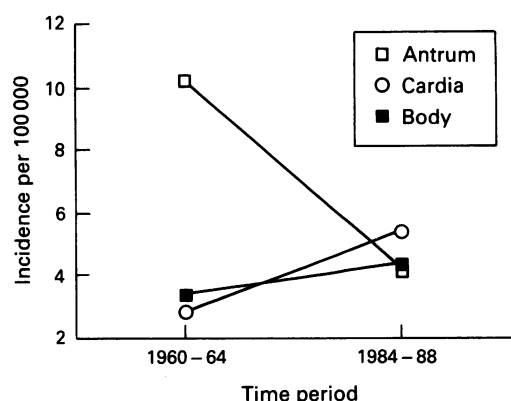


Figure 1: Changing incidence of gastric carcinoma analysed by site.

The population at risk was obtained from the Oxford Record Linkage Study to calculate crude annual incidence rates per 100 000 from 1964 to 1988. Gastric cancer rates were also age standardised to a 'world population' to allow appropriate comparison between the two time periods.²⁴

STATISTICAL ANALYSIS

The significance of means were studied using the Student's *t* test, and the Mann Whitney U-test for non-parametric values. The significance of proportions was tested using χ^2 test, and the Mantel-Heinzel χ^2 test for significance of the odds ratio was used to compare the effects of alcohol and tobacco consumption.

Results

INCIDENCE

The incidence of gastric cancer for men and women in the Oxfordshire region fell slightly from 18/100 000 inhabitants at the beginning of the 1960 decade to 15/100 000 inhabitants in the 1980s. These figures are similar to the incidence calculated in the west Midlands using independent data.⁶

When analysed by site, there was a marked fall in the incidence of antral tumours from 10 to 4.5/100 000 inhabitants between the two study periods, whereas the incidence of body and

cardia tumours increased from 3.3 to 4.2 and from 2.8 to 5.2/100 000 inhabitants respectively (Fig 1). The data were analysed for sex and age in each location (Table I). The greatest changes were seen in men. Detailed analysis by age was unreliable because of the small numbers. The changing prevalence of antral and cardia tumours was mostly seen in 45-64 year old men (data not shown).

Diffuse tumours (linitis plastica, or Borrmann IV) affecting more than one part of the stomach, accounted for 5.1% of the early series and 5% of the later.

AGE

The mean age (SD) of the 1984-88 series was significantly older than the mean age of the 1960-64 series (68.9 (11.3) *v* 63.3 (11.4), *p*=0.007) probably reflecting an ageing population. The mean age of patients with cancers of the cardia, however, was significantly younger than for the other sites (64.7 (11.0) *v* 70.0 (11.0), *p*=0.009) (Table I). In each site in both series, the mean age of the women was greater than the mean age of the men.

SEX RATIO

For all patients, there was a slight fall in the sex ratio (male/female) from 2.5:1 in the 1960-64 series to 2.2:1 in the 1984-88 series. The difference was not significant. When analysed for each site, however, there was a marked male predominance for the cardia site in both series. In the later series these ratios were 1.3:1 in the antrum, 2.1:1 in the body, and 3.7:1 in the cardia (antrum *v* cardia, *p*=0.001) (Table I).

HISTOLOGY

Tissue from 196 of 215 (91%) cases was available for histological study in the earlier series, and from 179 of 200 (89.5%) in the later series.

LAUREN CLASSIFICATION

The distribution of diffuse and intestinal type cancers was similar to that described by Lauren.²⁰ In the 1984-88 series, 38% of carcinomas were of type I (diffuse), 55.7% type II (intestinal), and 6.3% mixed. The distribution was similar in the 1960-64 series (39.6% diffuse, 51.3% intestinal, and 9.1% mixed).

These proportions remained unchanged when the data were analysed for sex and for site in both series.

DIFFERENTIATION

Table II shows that there was a small increase in the proportion of well and moderately differentiated tumours (6.1% and 9.5-24.5% and 33.0% for 1960s and 1980s respectively, and a corresponding decrease in the proportion of poorly differentiated tumours from the 1960-64 series to the 1984-88 series (69.4% and 57.5% respectively). When this was analysed by site, the proportion of moderately and poorly differentiated tumours significantly decreased (*p*=

TABLE I Gastric carcinoma: incidence * by sex, age and sex ratio by site

	Incidence	
	1960-64	1984-88
Antrum		
Men	6.9	2.4
Women	3.3	1.8
Age	64.39 (11.92)	70.00 (11.24) <i>p</i> =0.003
Sex ratio	2.1:1	1.3:1
Body		
Men	2.5	3.0
Women	0.9	1.4
Age	60.74 (12.1)	70.46 (10.66) <i>p</i> =0.001
Sex ratio	2.7:1	2.1:1
Cardia		
Men	2.1	4.2
Women	0.7	1.2
Age	60.45 (10.21)	64.78 (11.03) <i>p</i> =0.06
Sex ratio	3.1:1	3.7:1

*Incidence per 100 000 inhabitants, age:mean (SD), sex ratio: men: women.

TABLE II Tumour differentiation according to site

	Well differentiated		Mod differentiated		Poorly differentiated		Total	
	1960s n (%)	1980s n (%)	1960s n (%)	1980s n (%)	1960s n (%)	1980s n (%)	1960s n (%)	1980s n (%)
Antrum	7 (58.3)	8 (47.1)*	32 (66.7)	16 (27.1)‡	87 (64.0)	31 (30.1)‡	126 (64.3)	55 (30.7)
Body	3 (25.0)	6 (35.3)*	7 (14.6)	14 (23.7)*	27 (19.8)	33 (32.0)†	37 (18.9)	53 (29.6)
Cardia	2 (16.7)	3 (17.6)*	9 (18.7)	29 (40.2)‡	22 (16.2)	39 (37.9)‡	33 (16.8)	71 (39.7)
	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)
Total	12 (6.1)	17 (9.5)	48 (24.5)	59 (33.0)	136 (69.4)	103 (57.5)	196 (100)	179 (100)

Significance: *p=NS; †p<0.0045; ‡p<0.001.

0.001) in the antrum from the earlier to the later series, whereas the same relatively poorly differentiated tumours increased significantly in the cardia over the same periods. Furthermore, in the 1960–64 series, the proportion of moderately and poorly differentiated tumours in the antrum was significantly higher than in the body and the cardia (antrum *v* cardia, $p=0.001$) whereas in the 1984–88 series, the reverse was found (antrum *v* cardia, $p=0.001$).

GASTRITIS SCORE

In the 1980s series gastric mucosal specimens adjacent to the tumour were available for 143 of the 179 patients with gastric carcinoma, 33.6% of gastric cancer patients showed no evidence of chronic gastritis in the surrounding mucosa. Of the 66.4% with chronic gastritis, 39.1% showed chronic active gastritis, 23.8% chronic superficial gastritis, and 3.5% chronic atrophic gastritis. In the 1960s series, there was adjacent mucosa available from 145 of the 196 patients with gastric cancer. Twenty per cent showed no evidence of chronic gastritis, and of the 80% with chronic gastritis 53.8% showed chronic active gastritis, 19.3% chronic superficial gastritis, and 6.9% chronic atrophic gastritis (Table III).

In the 1980s series only 13% of antral tumours were surrounded by normal mucosa whereas this proportion was higher in cancers found in the body (28.2%) and especially in the cardia (53.5%) (antrum *v* cardia, $p<0.001$). On the other hand, the proportion of tumours associated with chronic active gastritis was highest in the antrum (60.9%) and was significantly lower in tumours affecting the body (46.1%) and the cardia (17.2%) (antrum *v* cardia, $p<0.001$). The results and significance were similar for the earlier series although more pronounced (Table III).

In the 1980s series, chronic active gastritis was associated more with tumours of Lauren's intestinal type (39 of 87, 44.8%) than with the diffuse type (20 of 55, 36.4%, $p=0.1$). The proportion of tumours associated with a normal

surrounding mucosa showed no significant differences between the two main types.

A similar relationship was seen in the 1960–64 series, chronic active gastritis was more associated with the intestinal type (44 of 79, 55.7%) compared with the diffuse type (29 of 61, 47.5%). The trend was not significant in either series.

INTESTINAL METAPLASIA

In the 1984–88 series, 52.1% of all gastric cancers were associated with intestinal metaplasia in the mucosa around the tumour. When studied by site, however, 82.5% of antral tumours were associated with intestinal metaplasia, compared with 23.5% of tumours of the cardia ($p=0.001$). In the 1960–64 series, 69.7% of all gastric tumours were associated with intestinal metaplasia. 79.8% of antral tumours were associated with intestinal metaplasia compared with 33.3% in the cardia ($p=0.001$).

The presence of intestinal metaplasia was related to the tumour type (Lauren classification). In the 1984–88 series the intestinal type was seen more often with intestinal metaplasia (46 of 74, 62.2%) compared with the diffuse type (20 of 50, 40%) ($p=0.01$). In the 1960–64 series, the relationship between intestinal metaplasia and intestinal type carcinoma was even more pronounced when compared to diffuse type tumours (83.8% *v* 51.8%, $p<0.001$) respectively.

HELICOBACTER PYLORI

In the 1960–64 series, the presence of *H. pylori* was identified in 37.5% of patients (54 of 144 available specimens). The proportion decreased in the later series to 25% (37 of 148 available specimens) ($p<0.046$). In the 1960–64 series 83.3% of carcinomas associated with *H. pylori* were situated in the antrum compared with 1.8% in the cardia ($p<0.001$). In the 1984–88 series, the proportion of *H. pylori* positive cases was 40% in the antrum compared with 32.5% in the cardia

TABLE III Distribution of gastritis according to site

	Antrum		Body		Cardia		Total	
	1960s n (%)	1980s n (%)	1960s n (%)	1980s n (%)	1960s n (%)	1980s n (%)	1960s n (%)	1980s n (%)
No gastritis	9 (9.2)	6 (13.0)	6 (24.0)	11 (28.2)	14 (63.6)	31 (53.5)	29 (20.0)	48 (33.6)
Chronic superficial gastritis	21 (21.4)	10 (21.8)	1 (4.0)	9 (23.1)	6 (27.3)	15 (25.9)	28 (19.3)	34 (23.8)
Chronic active gastritis	60 (61.2)	28 (60.9)	16 (64.0)	18 (46.1)	2 (9.1)	10 (17.2)	78 (53.8)	56 (39.1)
Chronic atrophic gastritis	8 (8.2)	2 (4.3)	2 (8.0)	1 (2.6)	0 (0.0)	2 (3.4)	10 (6.9)	5 (3.5)
Total	98 (100)	46 (100)	25 (100)	39 (100)	22 (100)	58 (100)	145 (100)*	143 (100)*

*51 cases missing from 1960s, and 36 from the 1980s.

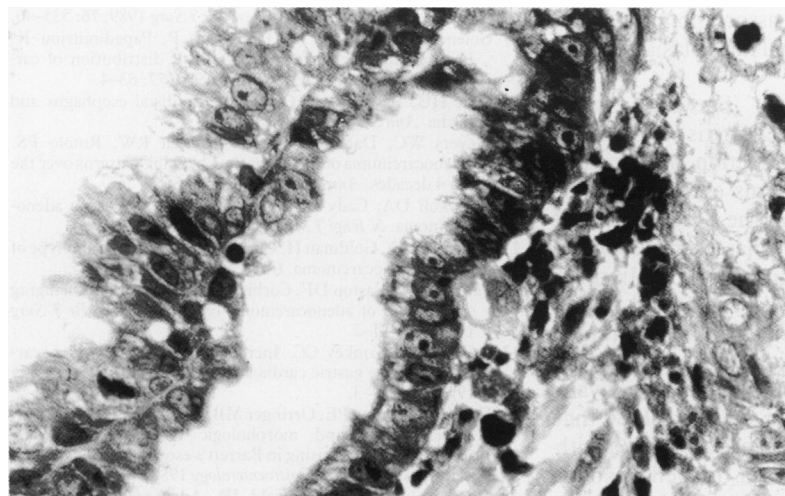


Figure 2: *Helicobacter* colonising a neoplastic gland from a well differentiated intestinal type adenocarcinoma of the pylorus. *H* and *E*.

($p=ns$). The difference between series was significant ($p<0.001$).

The presence of *H. pylori* correlated with the degree of inflammation. In both series, *H. pylori* was associated with chronic active gastritis (92.6% for the 1960s and 47.6% for the 1980s) compared with its presence in the mucosa without active inflammation (0% in the 1960s and 19% in the 1980s) ($p<0.001$).

H. pylori was particularly associated with the presence of intestinal metaplasia in both series (77.2% in the 1960s and 56.1% in the 1980s). The presence of *H. pylori* was related to tumour type according to the Lauren classification. *H. pylori* was more associated with the intestinal type in earlier and later series (59.1% and 48.1% respectively) than with the diffuse type (36.4% and 42.6%) but the differences were not significant. A noteworthy feature in both series was that the bacteria colonised not only the mucosa surrounding the tumour, but also the malignant glands of some cases of intestinal type carcinoma (Fig 2).

TOBACCO AND ALCOHOL CONSUMPTION

Of the 200 patients in the 1984–88 series, there were insufficient data on alcohol and tobacco consumption recorded in 70. Thus, relative risks were calculated on 130 patients.

Relative risks for gastric carcinoma in relation to alcohol and tobacco consumption are given in Table IV. There was a significant risk of tumours of the cardia for smokers (RR: 4.5, $p<0.001$), but alcohol did not appear to be a risk factor. Smoking appeared to be negatively associated with antral carcinomas (RR: 0.16, $p<0.001$).

TABLE IV Relative risk for gastric cancer according to site and alcohol and tobacco consumption

Smoke	Drink	Antrum <i>n</i> =39	Body <i>n</i> =35	Cardia <i>n</i> =56
No	No	25 (1)	12 (1)	12 (1)
No	Yes	3 (0.48)	3 (1.5)	3 (1.5)
Yes	No	6 (0.16)†	11 (1.1)	25 (4.5)†
Yes	Yes	5 (0.19)*	9 (1.3)	16 (3.5)*

n (rr); * $p<0.01$; † $p<0.0001$.

Discussion

A decrease in the incidence of gastric carcinoma has been widely reported over the last three decades.^{5–12} The magnitude of the decrease has varied from a fall of 88% in the white population of USA¹ to a much smaller decrease in Norway.²⁵ No satisfactory explanation has been found for this spontaneous decline although changes in the nitrosamine content of foods may be one factor.^{26, 27} Reports from Finland, Norway, and USA suggest that the declining incidence of gastric carcinomas is mainly because of a marked decrease in tumours of intestinal type.^{28–31} It is probable that the pathogenesis of the 'intestinal' type differs from the 'diffuse' type (defined by the Lauren Classification).²⁰ Thus, the high risk areas such as Japan, Chile, and Colombia have a predominance of intestinal type tumours whereas there are more diffuse tumours in the low risk areas such as USA and the UK.

In this study, the decrease in the incidence of gastric carcinoma over two decades was 17% which is similar to that reported from Birmingham.⁶ The incidence in the 1960s, however, might have been underestimated as endoscopic biopsy was not available and this study required histological verification rather than a radiological diagnosis. Another source of bias might be changing referral patterns within Oxfordshire. There was no evidence to support this and it would seem unlikely that the referral pattern would differ according to site of tumour.

Despite this declining incidence, several reports consistently show a rise in the incidence of carcinomas of the cardia.^{5–12, 16} This could be relative to a dramatic decrease in antral tumours^{10–12} but a number of studies, including the present one, suggest that the increase in proximal lesions is absolute.¹⁷ The increase was particularly seen in males with a rise in the male:female ratio from 3.1:1 to 3.7:1.^{10–15, 26, 27} Other studies have related antral carcinomas with lower social class, whereas tumours of the cardia have been associated with higher social class and with those of Caucasian origin.^{9, 13, 15} It was not possible, however, to obtain such data in this retrospective study.

Histological review of the tumours showed that the proximal lesions tended to be more poorly differentiated in the 1980s than in the earlier series. Although caution is required in retrospective interpretation, similar trends have been reported from Denmark and Boston^{11, 16} but not in all studies.^{7, 16, 17} In this study no difference was found in the proportion of diffuse and intestinal tumours between the two time periods and no relation was found between Lauren type and age, sex, stage or site. This is in agreement with previous studies.^{12, 13, 17, 28–30}

Perhaps the most striking finding in the present study was the histological analysis of the gastric mucosa surrounding the tumour. Only 13% of antral tumours were surrounded by histologically normal mucosa compared with over 50% of tumours in the cardia. In contrast, antral tumours mainly arose from mucosa showing the changes of chronic active gastritis. As reported in other studies,^{11, 12, 20} there was a predominance of intestinal type tumours associated with chronic inflammation in both time periods.

studied. The expected association between antral tumours and intestinal metaplasia was also seen.^{20 23 28-30}

The strong association between antral tumours and chronic active gastritis suggests the possibility that *H pylori* infection may have a pathogenic role. It now seems established that this organism is involved in the development of chronic inflammation and it has been associated with 19 to 80% of gastric carcinomas.³²⁻³⁷ In these reports the organisms have been found in the surrounding mucosa rather than in the tumour itself.³⁷ Despite the limitations of a retrospective study and the heterogeneity of the tissue available for review, the present findings show that over 80% of antral tumours were associated with *H pylori* in the 1960s although this fell to about 40% in the 1980s. In this later period *H pylori* was associated with a high proportion of cardia tumours and was found in 19% of patients with a normal surrounding mucosa.

One possibility for the decrease in antral carcinomas over time is a decrease in *H pylori* infection and hence a fall in the prevalence of chronic gastritis. This study cannot provide data to confirm or refute this hypothesis, however. If true, it should follow that antral cancer would be more common and would occur at an early age in those parts of the world where the majority of the population already have serum antibodies to the organism before adult life. Evidence from Colombia and Bolivia supports this hypothesis.³⁸⁻³⁹

In many series, smoking and/or alcohol has been associated with gastric cancer, and especially with cancer of the cardia.^{8 15-17 33-37 40-44} In the present study, cancer of the cardia was strongly associated with smoking whereas smoking and alcohol appeared to be negatively associated with antral tumours. Thus, the marked increase in tumours of the cardia may relate to past smoking habits, and may represent a cohort phenomenon as smoking increased between 1915 and 1950.⁴⁵

In conclusion, this study shows an absolute increase in the incidence of proximal gastric tumours in a defined population over a 20 year period. This has occurred when there has been a decline in antral tumours. Changes in the overall incidence of *H pylori* gastritis, as a result of rising standards of living and improved public health, together with past smoking habits, may partly explain these observations.

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